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Author: U.F. Gruber, Basel, Switzerland

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March 1969

Briefly and in summary, the course of the hemodynamic changes in the splanchnic region during severe shock can be represented as follows:

As a result of the decrease in the cardiac minute-volume (in surgery limited mostly to cardiogenic- or hypo-volemia), there is a relatively marked decrease in the time-flow volume with a significant increase in resistance (1, 56, 123). This is the result of the particularly strong adrenergic intervention and sensitivity of catecholamine in the splanchnic region in comparison with the other vascular flow regions (49, 60, 70, 90, 101, 107).

Hypoxic changes (64, 113), therefore, appear relatively early in a region low in  $O_2$  but with a high  $O_2$  consumption (13, 137). As a result, the  $O_2$  absorption can remain decreased in spite of restored flow even after transfusion (33, 125). Other regions, such as the liver, are able to convert immediately to aerobic metabolism.

As a consequence of these changes, large amounts of plasma are lost (87, 91, 93, 131) as a result of the increased permeability of the capillaries (97, 106). Under certain conditions, a temporary pooling can be observed in the upper intestinal regions (78, 80). In this regards, the erythrocytes become sequestered (55, 133) since the pre-capillary sphincters lose their tonus earlier than do the post-capillary ones (88). In this manner, the loss of volume, especially plasma volume, intensifies the hypovolemia in the sense of a positive feed-back mechanism (scheme).

Not all of these findings have been confirmed in humans. The partially contradictory results can be explained on the anatomical differences in the species tested, various means of narcosis, nature, severity, and duration of the shock model employed as well as by factors involving methodology (1, 16, 37, 44, 56, 108, 122, 128, 142). However, basically these mechanisms should follow the same course in laboratory animals and in humans.

As a result, it is understandable why several authors dealing with various forms of shock involving intestinal and liver bleeding and also chances of survival achieved favorable results after the administration of the following vaso-active substances:

Dibenzylamine (15, 54, 67, 80, 104, 131)

Chlorpromazine (72, 80, 121)

Isoproterenol (11, 79)

Phenylalanine-lysine-vasopressin (6, 7, 69, 68, 66, 95) not, however, in the case of the employment of catecholamines (11, 70, 75, 88, 98).

In this connection, good results have also been obtained by the use of low molecular weight dextrans (10, 38, 42, 43, 84, 129, 130, 133), celior block or denervation (17a, 104, 105, 110) and hypothermy (87) for amelioration of the intestinal perfusion and elimination of the state of shock.

The splanchnic region has a special significance in the event of shock when viewed from a hemodynamic view point. In this case, it is a question as to whether these circulatory factors are implicated in the secondary changes in the tissues which affect the entire organism and could be responsible for the more rapid onset of irreversibility before overall  $O_2$  deficit makes survival impossible.

In this regard, the following observations are presented:

I. In the upper intestine, there are significant pathological-anatomical alterations.

II. Resection of the intestines in rats and dogs during hemorrhagic (80, 97, 112) and endotoxic shock (48, 133) leads to a significant prolongation of the survival time. The only investigation (140) that led to a contrary conclusion has so many methodological errors that it does not have to be taken into consideration during this discussion.

III. An increase in the intestinal blood flow as a result of isolated perfusion of the arteria mesenterica superior (AMS) improves survival chances of animals undergoing shock (16, 86, 87, 93, 135).

Blattberg (29), however, made the assumption that the protective effect is not the result of perfusion as such since the animal's own blood is not effective. The donor blood must come from a healthy rabbit.

The results mentioned in I, II, and III, however, can only be explained on a hemodynamic basis and do not provide definite proof for the presence of specific intestinal factors.

Additional aspects are provided by the following facts:

IV. Since the entire intestinal tract represents a large reservoir of bacteria, microorganisms were considered very early as an essential element in shock pathogenesis. As early as 1944, J.C. Aub (14) in an extremely clear work explained that, in addition to loss of volume and bacterial factors, no other toxic components of any other kind could be found to explain the shock problem.

In the investigations of Fine (50,51) and his co-workers (54, 74, 104, 110, 115, 124, 131) (summarized in 53, 114), an attempt was made to attribute definite significance to endotoxin in the pathogenesis of irreversible shock. Although these comprehensive investigations stimulated thorough research into the shock problem, it has been assumed that very little significance can be attributed to endotoxin as being an important factor for the following reasons (67, 81, 103, 136):

(1) In germ-free animals, the shock proceeds in exactly the same manner as in ordinary animals (147).

Fine had argued that endotoxins were present in the food. However, the same reactions were observed in germ-free animals which had been fed a semi-synthetic food sterilized in a dry oven (41).

(2) The experiments of Fine have not been reproducible in other laboratories and pre-treatment with antibiotics has turned out to be unsuccessful even in his own hands (7, 24, 65, 76, 86, 96).

(3) Fine himself has shown that incubated aureomycin, which is practically without effect on microorganisms, will nevertheless protect against shock (74). Lin and Zweifach (89) assumed that antibiotics have a protective effect on the mucus membranes of the intestines and that this effect is unrelated to their bacteriostatic effect.

(4) Chloramphenicol, which is an effective antibiotic for gram-negative microorganisms, has no protective effect (74, 89).

(5) Mice, that have been made 10 times more sensitive to endotoxin, cannot be killed by the injection of blood of dogs irreversibly shocked with endotoxin (132).

(6) A hypotensive peptide has been detected in the cecum of germ-free rats (59). The amount of this substance decreases markedly upon the introduction of microorganisms (143). Certain bacteria, therefore, could exert a protective function (12, 41).

V. In the case of mechanical ileus, in addition to the loss of volume, bacteria or their products have also been implicated as responsible for the toxic properties of the peritoneal exudates and the intestinal contents (9, 7, 30). Ammundsen (8) also observed in germ-free rats a protein originating from the intestinal wall which increased toxicity. It was not hemoglobin or one of its derivatives. The results allow a comparison with the conditions during irreversible shock and indicate a possible participation of the intestinal wall.

Because the intestines and liver are dependent on each other anatomically and functionally, it seemed advisable to consider the latter also in our observations (5).

VI. Blockage of the reticulo-endothelial system (RES) increases the sensitivity to shock (145). During shock, the ability of the RES to eliminate endo-

toxin from the blood is decreased (115, 144). Also, its ability to eliminate bacteria (50) and colloid particles (23, 146) is diminished. This impairment of the so-called granulopeltic activity is considered by many authors to be a significant factor in shock pathogenesis (3, 27, 53, 147). In that regards, one must also consider substances which block the RES to be hepato-toxic.

Administration of citrated blood increases the limited detoxifying function of the RES (109) and it was shown earlier that citrate in vitro influences the activity of leucocytes (2).

In addition, vasoactive substances such as histamines, serotonin, and bradykinin, depending on dosage, restrict the function of the RES (27).

Furthermore, there is the question whether the large quantity of denatured proteins and cell aggregates in transfused blood can restrict the blood supply of the liver by increasing viscosity and in this manner restrict its function (141).

Blattberg and Levy have assumed that in the course of severe shock, a RES depressor substance (RES-DS) is produced in the gastrointestinal tract and enters the system via the portal vein (22, 25). This material is formed during AMS shock (arteria mesentericum superior occlusion) in the rat and in the dog (24, 25) as well as during hemorrhagic shock in the dog (21-23). The RES-DS can be transmitted via various carriers (blood, plasma, plasma-dialysate) from rat to rat and from rat to dog. On the basis of chromatographic separations and purifications, it appears to a small molecule. Its mechanism of action does not involve blockage of the RES (26).

Levy and Blattberg and co-workers (9, 28, 18, 20, 85) have found that in the post-transfusion phase after hemorrhagic shock in the dog, the immune system becomes involved. This appears to ultimately correlated with damage to the RES function.

Various authors have assumed that during severe shock, there is no formation of enterotoxins but that the liver loses its ability to inactivate metabolites which are normally present (15, 41, 80, 113).

Blattberg (23) and Lillehei (86) have demonstrated that perfusion of the liver does not have any effect. On the other hand, chlorpromazine and dibenzylin improve chances of survival only as long as the liver is present (15, 80, 86, 121).

VII. Bounous and co-workers (33) (summarized in 62) after extensive examinations believe that the metabolism of the mucous membranes of the intestines and the production of protective mucin are affected before pathological-anatomical alterations can be observed and before other regions show similar changes (35, 34, 31, 36). These investigators were able to demonstrate that purification of isolated coils of the intestine or prophylactic administration of trasylool inhibited the typical symptoms of hemorrhagic necrosis from appearing during irreversible shock in the dog and the rat (34, 32). They assumed that trypsin and chymotrypsin have a special significance but pointed out there is much less trypsin present in the human intestine. The prophylactic ligation of the pancreatic ducts also has a protective effect on the intestines and prolongs survival time. Therefore, it is possible that toxic products of the intestinal constituents pass through the previously damaged mucous membranes (see E.E. Smith, Surg. Gynec. Obstet. 125: 45 (1967)).

VIII. Burri and Allgower (39, 40) found a toxic substance in the intestinal walls of burned animals and in animals with hemorrhagic shock. This factor is active against mice which are refractive to endotoxin. They assumed that it was formed during the hypoxic phase in the intestinal wall.

The results mentioned in V - VIII do not present absolute evidence for the formation of toxic substances in the intestinal tract or for a decreased function of detoxification of the liver. There are many gaps - severe controls, too small amounts of experimental material, missing statistical evaluations, confirmation

in other animals by other authors, and lack of data for humans. Nevertheless, they certainly deserve our full attention.

For purposes of studying intestinal factors during irreversible shock, many investigators in recent years have employed the so-called AMS shock model:

In rats (6, 7, 41, 89, 121)

In dogs (76, 77, 96, 105, 131)

In rabbits (15, 24, 67, 81, 82, 91, 94, 105, 116, 119, 127, 138)

TABLE I

Survival times, Rabbits  
Total Ligature of the  
AMS

n = 10

9 ± 3 hr

Several experiments on anaesthetized (pentobarbital) rabbits; dorsal, retro-peritoneal access, ligature with 000 silk.

TABLE 2

Survival times, rabbits  
↳ standard AMS occlusions  
+ opening

n = 10

1½ hr (10 min to 3 hr)

see table 1. The survival time after ligature and reopening of the AMS closure is shorter than in the case of total ligature.

Simple ligature leads to death with all of the species within a few hours (table 1). Why? If the AMS is closed off for a few hours and afterwards the closure is released, death occurs earlier than without this procedure (Table 2). This situation corresponds closely to the hemodynamic conditions during severe shock. The significance of the loss of volume in this case can be seen in Table 3.

TABLE 3

Hematocrit, Rabbits	
4 standard AMS occlusions	
+ opening	
initial:	39.0 (n = 18)
4 hr:	47.5 (n = 18)
45 min:	55.0 (n = 7)
90 min:	56.5 (n = 5)

There were great losses of plasma during the occlusion phase. This became even worse after the reopening. The animals lost about 50 % of their plasma volume with 1 - 2 hours after reopening.

$$\text{Plasma volume loss in percent} = 1 - \frac{\text{Hct}_1 \times \text{Pct}_2}{\text{Hct}_2 \times \text{Pct}_1} \times 100$$

Pct = plasmacrit

Several investigators have made a great effort to explain the reasons for this phenomenon. The various substances listed in Table 4 have a possible causal significance in the rapid destruction of circulation during hemorrhagic and AMS shock.

It is quite likely that the interstitial fluids are likewise reduced. This explains the significance of the loss of volume.

In order to prove the some or several of the substances mentioned in Table 4 play an important role in eliciting irreversible changes during shock, the following criteria were necessary in my opinion:

- (1) Isolation and identification of the toxic substance in the portal vein and in the peripheral blood. If the latter is not possible, one should at least be able to show the destructive effect of the toxic substance in the liver or in the RES.
- (2) Determination of the area of formation of the toxin and explanation of its mechanism of action.
- (3) Proof that the toxic substance is effective and attributes significantly to death in the case of proven normovolemia.

TABLE 4  
Possible Enterotoxins

Substance	Author	Reference	Year published
VEM-VDM	Sherr	(134)	1965
Ferritin	Baez	(15)	1961
Vasodepressor substance	Hershey	(66)	1961
Vasodepressor substance	Selkurt	(126)	1963
Noradrenalin inhibitor	Paez	(15)	1960
Hypotensive peptide	Gorjon	(59)	1965
Vasoactive polypeptide	Kobold	(82)	1963
Vasoactive substance	Peters	(111)	1964
Vasotoxic substance	Selkurt	(127)	1969
Dilator + Constrictors	Rothie	(120)	1961
Catecholamine	Kobold	(82)	1963
5-hydroxytryptamine	Baez	(15)	1961
Serotonin	Janoff	(76)	1961
Serotonin	Kobold	(81)	1962
Serotonin	Kobold	(82)	1963
Histamine	Kobold	(82)	1963
Trypsin	Bounous	(33)	1964
Chymotrypsin	Bounous	(33)	1964
Kalligrein	Kobold	(81)	1962
Cathepsin	Janoff	(77)	1962
Cathepsin-like acid proteinase	Reich	(116)	1965
Acid phosphatase	Janoff	(77)	1962
Beta-glucuronidase	Janoff	(77)	1962
DNase	Jancif	(77)	1962
RNAase	Janoff	(77)	1962
Hemoglobin degradation products	Nemir	(107)	1959
potassium	Mavor	(94)	1964
Endotoxin	Fine	(50)	1955
Exotoxin	Aub	(14)	1943
Intestinal Wall factor	Burri	(39)	1965

(4) Transferability of the toxic principle to another animal, for example, by injection, transfusion, or by crossed (systemic) circulation.

In these cases, the shocked animal does not have to die since a healthy organism can eventually combat the toxin successfully. It appears, therefore, possible that the substances in question have been examined several times in animals undergoing reversible shock. They can also be tested after liver damage produced by RFS blockage for example. In this regards, one must consider that since likely the vasoconstrictor control has to be also influenced if a vasoactive substance should lead to the collapse of the circulatory system.

Thus far, no investigator has been able to fulfill all of these criteria.

ad 1. Of the substances mentioned in Table 4, it is most likely that the vasoactive ones are the ones which are the toxins. The effect is probably due to a mixture of vasoconstrictive as well as vasodilatative substances. At present, there is not evidence available (for serotonin, see (118)).

ad 2. The fact that such substances are present in the blood of the portal vein is uncontestable. On the other hand, there is still the question as to whether they are derived from the intestinal wall or intestinal contents. Also there is still the question as to which of kinds of cells they originate from (see tables 5 and 6).

ad 3. An extremely small number of investigators have considered the significance of the volume factor. From the plasma volume and hematocrit determinations carried out by various authors (41, 44, 93, 121, 131), it is assumed that in the intestinal tract, the whole plasma volume can disappear into the wall or into the lumen. Only strict volumetric controls can be used as proof for mechanisms other than the loss of plasma. It is possible to conceive that ultimately toxins that happen to be present intensify the loss of plasma.

ad 4. The transportation of a toxic principle during hemorrhagic shock has been demonstrated in rabbits (103, 124,) and in dogs (115, 124).

Janoff (76) was able to detect a toxin in the blood of the portal vein of rabbit undergoing AMS shock but not in the plasma.

TABLE 5

Portal vein blood, rabbit  
4 hours of AMS occlusion + opening  
n = 7 controls = 2

Mortality/ n mice	
Occl.	controls
14/61	2/18

The blood of the portal vein was removed with a sterile syringed immediately after opening the AMS occlusion and injected into mice intraperitoneally in quantities of 10 % of the KG weight. We were not able to demonstrate more toxicity in the blood of the portal vein of the experimental animals as compared to the control animals.

TABLE 6

Carotis blood, rabbits  
4 hours AMS occlusion + opening  
n = 4 controls n = 4

	Mortality/ n mice	
	occlusion	control
Normal mice	1/17	2/25
RES mice	0/25	1/36

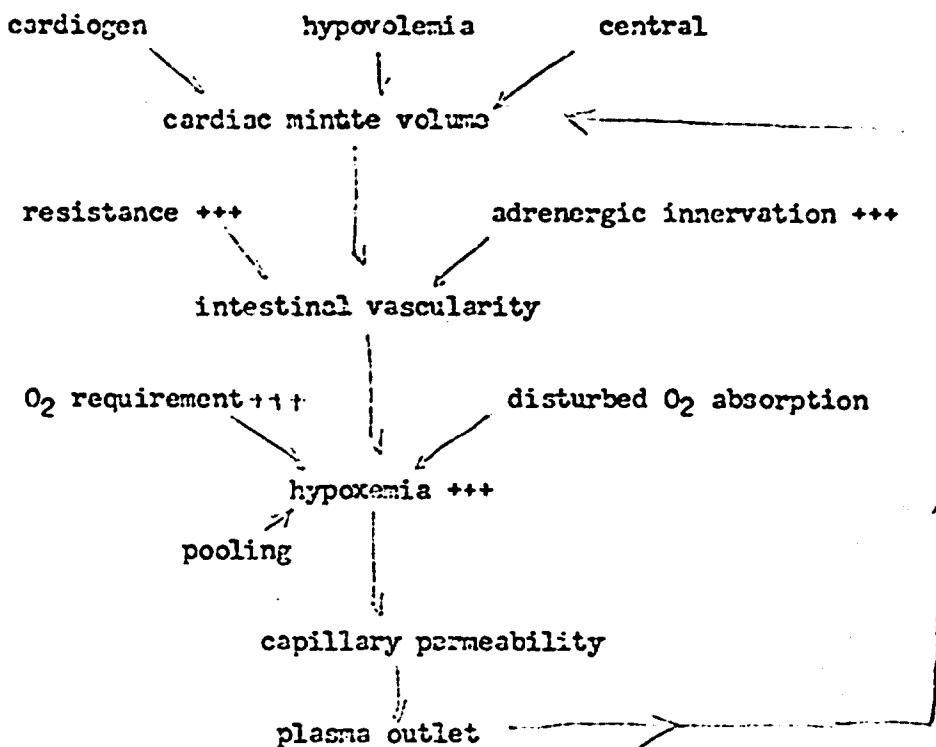
For procedure, see table 5. Toxicity of the peripheral blood could not be detected after injection into RES blocked mice. It is possible that the toxins are so unstable that they lose their activity very quickly. Technics and the time when the blood was taken could explain the differences between these and the results published in the literature.

Tice (138) after AMS shock found a toxic factor in the ductus thoracicus lymph of the dog. The injection of such lymph into rabbits whose RES had been blocked by means of thorotраст, led to death of the animals. The circulation of the lymph has certainly not been given sufficient consideration in the study of shock.

### CONCLUSIONS

The consequence of the hemodynamic disturbances in each massive decrease in the cardiac time-volume are especially severe in the splanchnic region as compared to the other vascular flow regions even after transfusion. Also, they appear earlier. The loss of volume in the intestinal tract is especially large due to anoxic damages. However, these circulatory alterations alone cannot be used to completely explain the appearance of irreversibility; suitable validations are not available at this time.

Schematic summary of the hemodynamic changes in the splanchnic changes in shock. The importance of the loss of volume becomes evident.



Scheme: Positive feed-back mechanism.

It is very likely that basoactive substances from the intestinal tract travel to the liver via the blood of the portal vein whereby the liver and the RES particularly are injured by the vassotoxin or other noxious substances

during detoxification and phagocytosis. This would explain the effect on the whole organism that is observed.

The bacterial factor, especially endotoxin, if at all, will play a significantly smaller role in hypovolemic shock than has been assumed in the past. This does not mean, however, that bacterial factors are not essential in septic shock! It should also be mentioned that many authors have employed endotoxin in the laboratory to simulate shock. This should not be interpreted as meaning that endotoxin plays a major role in the initiation of irreversible shock.

In our experiments, we could not demonstrate a specific toxicity for homogenates prepared from the intestinal walls of rabbits in AMS shock. The material was injected into both normal and RES-blocked mice (Tables 7-10).

TABLE 7

Intestinal wall homogenate  
+ AB  
6 hours = AMS ligature  
rabbits n = 8  
injected into mice  
mortality: 0 % (n = 85)

mortality of mice after i.p. injection of fresh small intestinal wall homogenate with and without the addition of tetracycline (1 mg/2ml). Amount of homogenate injected was 10 % of the Kg weight.

TABLE 8

Intestinal wall homogenate, sterile  
8 hours AMS ligature  
rabbits: n = 8, controls n = 9  
injected into mice  
mortality: 26 % (n = 100)  
controls: 21 % (n = 130)

Mortality in mice after i.p. injection of a 10 % suspension of small and large intestinal wall homogenate after lyophilization and sterilization with ethylene chloride. Technic in (39, 40).

TABLE 9

Intestinal wall homogenate,  
sterile  
4 hours AMS occlusion + opening  
rabbits n = 6 controls n = 11  
injected into mice  
mortality: 74 % (n = 137)  
controls: 41 % (n = 300)

Mortality in mice after injection of a 10 % suspension of the small and large intestinal walls (sterilized according to the procedure described in Table 8). The increase in mortality is not significant since there were large deviations in both groups (in some series of experimental animals there was no mortality while in some of the control groups, there was a high mortality).

CONSEQUENCES FOR THE PRACTICE

The results mentioned above also have significance in practical surgery (73, 83), that is, firstly, in the treatment of acute (embolies) (58), thrombotic (4) and arteriosclerotic (20, 45, 46) (angina abdominalis) compressions of the AMS. In addition, there is no reason to doubt that intestinal necroses without detectable pathological-anatomical alterations of the vessels also occur in tumors (37a, 99, 102) as well as in shock (71, 92, 93). On occasion in certain cases, there is a connection with digitalis intoxication (11a). Mesenteric infarctions occur in 2 % of all ileus cases (47) or in 0.2 % of all surgical cases (93). Even today, the mortality approaches 90 % (47, 93, 139). A procedure for treating intestinal gangrene with the most success has not yet been elucidated. Whether an immediate surgical restoration (61) of the circulation with actual closure of the AMS represents the best therapy in all cases is still much doubted (52) since, after opening an acute AMS occlusion, a circulation collapse is practically unavoidable. Apparently, massive infusion therapy is effective only in a very few cases. The extent of the diminution of the blood flow and the duration of the disturbance appear to be important factors. These factors are very difficult to evaluate. It is therefore necessary in case of mesenteric infarctions to

consider treatment by isolated perfusion of the AMS region (94), the performance of a splanchnic blockade (52, 104) and/or the use of chlorpromazine, ditenzylin, and hypertonic solutions of low-molecular-weight dextrans (see table 10). It is sure that in all cases, large amounts (2-3 liters or more) of plasma and dextran should be administered. As far as the use of vasoactive substances are concerned, such as octapressin, with regards to humans, there is not enough information available (66). In a case of a simple intestinal necrosis, only a surgical intervention (resection plus eventual vascular operation) has any chance of success.

TABLE 10

Incomplete series of tests for determining whether various techniques for refining intestinal wall homogenates exert an influence on their toxicity after injection into mice. Three rabbits were submitted to a 4 hour AMS occlusion and their intestines were treated in various ways after the reopening of the occlusion. The intestines of two healthy, control animals were treated in the same manner. From these experiments, no conclusions can be drawn concerning the influence of time and temperature.

Treatment	Occlusion		Control	
	number of mice	Mortality %	Number of mice	Mortality %
Immediate injection	30	0	30	0
4 hours deep frozen	--	--	10	0
4 hours at 4°C	10	0	--	--
1 hour at 18°C	20	5	10	0
2 hours at 37°C	--	--	10	0
4 hours at 37°C	--	--	10	0
Total intestine 4 hours, 37°C, lyophilized at once and sterilized	10	0	--	--
After 30 min, lyophilized and sterilized	10	0	--	--
After 60 min, lyophilized and sterilized	10	0	--	--

SUMMARY

The splanchnic region has an essential significance in severe shock as the effects of hemodynamic disturbances appear very early and are very pronounced. The danger of irreversible damages is especially great (circ. vitirosus) before they can be detected in other vascular regions. This leads to large losses of plasma as a result of anoxic alterations in the intestinal tract. It is very likely that vasoconstrictive as well as vasodilatory substances travel from the intestinal contents or from the intestinal wall into the portal vein and damage the liver. They may be also responsible for the impairment of the functions of the reticuloendothelial system. This does not appear to be the result of endotoxins. Among the numerous substances that have been considered as possible intestinal toxins, none have been isolated or identified as a causative agent. Their significance in human shock is still not clear.

The hemodynamic alterations in the splanchnic region, as they occur in irreversible shock, are capable of being reproduced in the arteria mesenterica superior (AMS) shock model. The information obtained from this model has practical clinical significance in the treatment of mesenteric blood flow disturbances, especially in mesenteric infarctions, in which case it is considered that in humans, at least two arteries must have inferior blood flow before clinical symptoms appear. These aspects are probably more frequent than generally assumed. Intestinal gangrene without any detectable organic necroses in the AMS region can also occur in humans. It is questionable whether an immediate vascular surgical restoration of the intestinal blood flow in cases of actual occlusion is the best therapy except when there is a clear necrosis. Isolated perfusion of the AMS region, administration of chlorprussic acid, dibenzylin, octopressin, and low-molecular-weight dextrans, coloacal blockade, have to be considered. The

most important treatment, however, is sufficient replacement of plasma. Several liters of plasma may be necessary.

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